REMARKS

I. Status of the Claims

Claims 1-57 are pending in the application. Claims 17-19, 22, 41-43, 46 and 49-55 stand withdrawn pursuant to a restriction requirement, and thus claims 1-16, 20, 21, 23-40, 44, 45, 47, 48, 56 and 57 are under examination and stand rejected

II. Objections

Claims 15, 20, 39 and 44 are objected to as containing non-elected embodiments. As these claims comprise subject matter that is subject to rejoinder, deferral of the objection is requested.

Claim 27 is said to be a substantial duplicate of claim 28. Claim 28 has been amended to distinguish it's subject matter from that of claim 27.

III. Rejections Under 35 U.S.C. §112, First Paragraph

A. Enablement

Claims 1-16, 20, 21, 23, 25-40, 44, 45, 47, 56 and 57 are rejected as lacking enablement for anything other than a bispecific antibody comprising SEQ ID NO:1, wherein the antibody binds specifically to CD3 and EpCAM. Applicants traverse.

Initially, the examiner presents a convincing argument that modification of CDRs from antibodies can have very dramatic effects on the binding properties of those antibodies. Indeed, the present claims do pose a large number of possible CDR combinations, and which combinations of CDRs will provide useful antibodies is *a priori* unclear. However, this is the extent of applicants agreement with the examiner, as explained further below.

Enablement requires the skilled artisan to know how to make and use the present invention. First, with regard to making, it seems the examiner is arguing that the specification contains insufficient guidance on making when it is argued that specific operable CDRs and CDR combinations are not identified. However, that is not the ***only*** way enablement is achieved. It is also possible, as is the case here, that one can screen any putative bispecific antibody according to the methodology provided in the examples to identify those antibodies that are functional. Thus, it is quite untrue that "the specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims."

The other prong of enablement, how to use, seems to be implicated by the examiner's other argument, namely, that the claims are overly broad in encompassing many antibodies that will lack the desired functionality. However, both claims 1 and 25 contain functional restrictions that ***exclude*** inoperative species, exemplified in claim 1 below:

> ... a first portion of the bispecific antibody is capable of recruiting the activity of a human immune effector cell by ***specifically binding to an effector antigen located on the human immune effector cell***, said first portion consisting of one antibody variable domain; and
>
> a second portion of the bispecific antibody is capable of ***specifically binding to a target antigen other than the effector antigen***, said target antigen being located on a target cell other than said human immune effector cell, and said second portion comprising two antibody variable domains.

Thus, this is not the simple case of a fatally overly broad claim, but one where inoperative species are not included. Where applicants have limited the scope of the claims to the area where operability has not been properly challenged, maintenance of the rejection is improper. *In re Frillette*, 165 USPQ 259 (CCPA 1970); *In re Buting*, 163 USPQ 689 (CCPA 1969).

For these reasons, applicants submit that the rejection for lack of enablement is improper and respectfully request that it be withdrawn.

B. Written Description

Claims 1-16, 20, 21, 23, 25-40, 44, 45, 47, 56 and 57 are rejected as lacking written description for binding specificity of all bispecific antibodies, variable domains in a first CDR and variable domains in a second CDR from any antibody. Applicants traverse.

As explained recently by the Federal Circuit, there is no *per se* requirement under written description that a specification contain a detailed discussion of genetic elements where those elements are well known to those in the field:

> The Board stated that "controlling precedent" required inclusion in the specification of the complete nucleotide sequence of "at least one" chimeric gene. Bd. op. at 4. The Board also objected that the claims were broader than the specific examples. Eshhar and Capon each responds by pointing to the scientific completeness and depth of their descriptive texts, as well as to their illustrative examples. The Board did not relate any of the claims, broad or narrow, to the examples, but invalidated all of the claims without analysis of their scope and the relation of claim scope to the details of the specifications.
>
> Eshhar and Capon both argue that they have set forth an invention whose scope is fully and fairly described, for the nucleotide sequences of the DNA in chimeric combination is readily understood to contain the nucleotide sequences of the DNA components. Eshhar points to the general and specific description in his specification of known immune-related DNA segments, including the examples of their linking. Capon points similarly to his description of selecting DNA segments that are known to express immune-related proteins, and stresses the existing knowledge of these segments and their nucleotide sequences, as well as the known procedures for selecting and combining DNA segments, as cited in the specification.
>
> Both parties argue that the Board misconstrued precedent, and that precedent does not establish a *per se* rule requiring nucleotide-by-nucleotide re-analysis when the structure of the component DNA segments is already known, or readily determined by known procedures. The "written description" requirement implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed. See *Enzo Biochem*, 296 F.3d at 1330 (the written description requirement "is the *quid pro quo* of the patent system; the public must receive meaningful disclosure in exchange for being excluded from practicing the invention for a limited period of time"); *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345-46 (Fed. Cir. 2000) (the purpose of the written description requirement "is to ensure that the scope of the right to exclude . . . does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification"); *In re Barker*, 559 F.2d 588, 592 n.4

(CCPA 1977) (the goal of the written description requirement is "to clearly convey the information that an applicant has invented the subject matter which is claimed"). The written description requirement thus satisfies the policy premises of the law, whereby the inventor's technical/scientific advance is added to the body of knowledge, as consideration for the grant of patent exclusivity.

The descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. The law must be applied to each invention that enters the patent process, for each patented advance is novel in relation to the state of the science. Since the law is applied to each invention in view of the state of relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science.

For the chimeric genes of the Capon and Eshhar inventions, the law must take cognizance of the scientific facts. The Board erred in refusing to consider the state of the scientific knowledge, as explained by both parties, and in declining to consider the separate scope of each of the claims. None of the cases to which the Board attributes the requirement of total DNA re-analysis, *i.e.*, *Regents v. Lilly*, *Fiers v. Revel*, *Amgen*, or *Enzo Biochem*, require a re-description of what was already known. In *Lilly*, 119 F.3d at 1567, the cDNA for human insulin had never been characterized. Similarly in *Fiers*, 984 F.2d at 1171, much of the DNA sought to be claimed was of unknown structure, whereby this court viewed the breadth of the claims as embracing a "wish" or research "plan." In *Amgen*, 927 F.2d at 1206, the court explained that a novel gene was not adequately characterized by its biological function alone because such a description would represent a mere "wish to know the identity" of the novel material. In *Enzo Biochem*, 296 F.3d at 1326, this court reaffirmed that deposit of a physical sample may replace words when description is beyond present scientific capability. In *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1332 (Fed. Cir. 2003) the court explained further that the written description requirement may be satisfied "if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." These evolving principles were applied in *Noelle v. Lederman*, 355 F.3d 1343, 1349 (Fed. Cir. 2004), where the court affirmed that the human antibody there at issue was not adequately described by the structure and function of the mouse antigen; and in *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 925-26 (Fed. Cir. 2004), where the court affirmed that the description of the COX-2 enzyme did not serve to describe unknown compounds capable of selectively inhibiting the enzyme.

The "written description" requirement must be applied in the context of the particular invention and the state of the knowledge. The Board's rule that the nucleotide sequences of the chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known, is an inappropriate generalization. When the prior art includes the nucleotide information, precedent does not set a *per se* rule that the information must be determined afresh. Both parties state that a person experienced in the field of this invention would know that these known DNA segments would retain their DNA sequences when linked by known methods. Both parties explain that their invention is not in discovering which DNA segments are related to the immune response, for that is in the prior art, but in the novel combination of the DNA segments to achieve a novel result.

> The "written description" requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution. Both Eshhar and Capon explain that this invention does not concern the discovery of gene function or structure, as in Lilly. The chimeric genes here at issue are prepared from known DNA sequences of known function. The Board's requirement that these sequences must be analyzed and reported in the specification does not add descriptive substance. The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes.

Applicants further highlight a quote from the preceding passage: "None of the cases to which the Board attributes the requirement of total DNA re-analysis, *i.e.*, *Regents v. Lilly*, *Fiers v. Revel*, *Amgen*, or *Enzo Biochem*, require a re-description of what was already known." Here, the examiner is making a similar requirement – that applicants provide a re-description of known CDRs – and does so based on similar case law. And just as the Federal Circuit found with respect to the Board decision in the *Capron* case, that requirement is improper.

Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

IV. Rejections Under 35 U.S.C. §102

Claims 1-3, 7, 8, 13-16, 20, 21, 23, 25-20, 31, 32, 37-40, 44, 45 and 47 stand rejected as anticipated by Mack *et al.* (1995), and the same claims plus claims 11, 13, 35 and 36 stand rejected as anticipated by Mack *et al.* (1997). Applicants traverse, but in the interest of advancing the prosecution, the claims have been amended to more clearly distinguish the present invention from the disclosure of Marks *et al.* In particular, Mack *et al.* (1995) and Mack *et al.* (1997) describe a bispecific single chain with four variable domains: One scFv (VL-VH) is specific for EpCAM, the other scFv (VH-VL) for CD3. News claims 1 and 25 relate to a bispecific antibody with a total of ***three*** antibody variable domains: one variable domain binds

to an effector antigen on the human effector cell, whereas the other two variable domains bind to the target antigen on a target cell. This embodiment is described, for example, at page 8, first and second paragraphs of the specification as filed, as well as in original claims 2 and 26. In light of the amendment to the claims, applicants submit that the claims presented for reconsideration and clearly novel over the cited art, and therefore reconsideration and withdrawal of the rejection is respectfully requested.

V. Rejections Under 35 U.S.C. §103

A total of nine different rejections are advance under §103 over most of the pending claims, where each rejection relies on the Mack *et al.* references cited above in the section addressing novelty rejections. Applicants traverse each of these rejections.

Again, as presented for reconsideration, the present invention relates to a bispecific antibody with three variable domains. As shown in the Examples of the present application, a cytotoxically-active bispecific antibody with three antibody variable domains could be successfully produced in prokaryotes. Mack *et al.* (1995) and Mack *et al.* (1997) describe a bispecific single chain antibody with four variable domains. The references fail to teach or suggest a 3-variable domain bispecific antibody as claimed in amended claims 1 and 25, and none of the supporting references cures this defect. As such, a *prima facie* case cannot stand given that an explicit element of the presently claimed invention is missing from the prior art.

Furthermore, the cited references actually teach away from generating a 3-domain bispecific antibody. For example, on page 7023, right column, of Mack *et al.* (1995) the authors state:

> Although periplasmic expression in *E. coli* is known to yield functional sc-Fv fragments (20), consisting of two immunoglobulin V domains, addition of a third or fourth V domain by using peptide linkers completely abolished binding activity of periplasmic preparations, despite the presence of recombinant protein in sufficient amounts (data not shown). This shows that the periplasm of *E. coli* is insufficient for functional expression of these antibody derivatives containing more than two immunoglobulin domains on a single polypeptide chain.

In light of this statement, there is no motivation to even attempt a modification of Mack *et al.* (1995) or Mack *et al.* (1997), with or without the other references cited by the examiner, that would result in the presently claimed bispecific antibody with three variable domains. And even if one were so motivated, there clearly would be no reasonable expectation of success.

Thus, applicants respectfully submit that all of the advanced obviousness rejections are improper as lacking each element of a *prima facie* case, namely, (a) a teaching of each element of the claimed invention, (b) a motivation to modify the prior art to arrive at the claimed invention, and (c) a likelihood of success. In re O'Farrell, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988).

VI. Conclusion

In light of the foregoing, applicants submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. The Examiner is invited to contact the undersigned attorneyat (512) 536-3184 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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